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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/522,278	03/09/2000	Peter Francis Joseph O'Hare	5759-54451	3028

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EXAMINER
ZARA, JANE J

ART UNIT	PAPER NUMBER
1635	23

DATE MAILED: 06/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

File

Office Action Summary

Application No.	Applicant(s)
09/522,278	O'Hare et al
Examiner	**Art Unit**
Jane Zara	1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Mar 7, 2003* .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-22* is/are rejected.

7) ☒ Claim(s) *23* is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☒ None of:

1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

This Office action is in response to the communication filed March 7, 2003.

Claims 1-23 are pending in the instant application.

Continued Prosecution Application

The request filed on March 7, 2003 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/522,278 is acceptable and a CPA has been established. An action on the CPA follows.

Priority

Acknowledgment is made of applicant's claim for foreign priority based on applications filed in Great Britain on December 24, 1999 and March 10, 1999 on . It is noted, however, that applicant has not filed certified copies of the applications as required by 35 U.S.C. 119(b).

Response to Arguments and Amendments

Any rejections not repeated in this Office action are hereby withdrawn.

New Rejections

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-3, 10, 17, 18, 20 and 21 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4, 6, 7, 16-18 of WO 97/05265 . Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the instant application are drawn to compositions and methods for the delivery of substances to cell in vitro comprising aggregated compositions and methods of

making aggregated compositions comprising combining in solution a VP22 polypeptide or a fragment thereof having a transport function of VP22 (and which optionally comprise amino acid sequences 159-301 of SEQ ID NO: 12), a protein, polypeptide, nucleic acid polynucleotide or oligonucleotide to be transported via VP22, associated either covalently or non-covalently, and optionally encapsulated within a liposome for delivery into target cells in vitro and a pharmaceutically acceptable excipient, which aggregated composition has a particle size between 0.1 and 5 microns, whereby a solution comprising the VP22 polypeptide and polypeptide or oligonucleotide is mixed in solution and is delivered to cells in vitro and the claims of WO 97/05265 are drawn to compositions and methods comprising combining in solution and delivering VP22 transport polypeptide or an active portion thereof, in non-covalent or covlent association with a non-peptidyl substance to be transported, whereby the substance is delivered to a target cell in vitro, and which compositions further comprise a liposomal delivery agent, (whereby the solution is aggregated upon mixing, and its particle size is between 0.1 and 5 microns).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1-3, 10, 17, 18, 20 and 21 are rejected under 35 U.S.C. 102(b) as being anticipated by O'Hare et al.

O'Hare et al (WO 97/05265) teach aggregated compositions and methods of making aggregated compositions comprising a VP22 polypeptide or a fragment thereof having a transport function of VP22 (and which optionally comprise amino acid sequences 159-301 of SEQ ID NO: 12), a protein, polypeptide, nucleic acid polynucleotide or oligonucleotide to be transported via VP22, associated either covalently or non-covalently, and optionally encapsulated within a liposome for delivery into target cells in vitro and a pharmaceutically acceptable excipient, which aggregated composition has a particle size between 0.1 and 5 microns, whereby a solution comprising the VP22 polypeptide and polypeptide or oligonucleotide is mixed in solution and is delivered to cells in vitro (See especially pages 4-7 and claims 1-4, 6, 7, 16-18).

Claims 1-3, 15, 16, 18, 20, 21 are rejected under 35 U.S.C. 102(e) as being anticipated by O'Hare et al.

O-Hare et al (USPN 6,184,038) teach aggregated compositions and methods of making aggregated compositions comprising a VP22 polypeptide or a fragment thereof having a transport function of VP22 (and which optionally comprise amino acid sequences 159-301 of SEQ ID NO: 12), an oligonucleotide of at least 10 nucleobases, a pharmaceutically acceptable excipient, which aggregated composition has a particle size between 0.1 and 5 microns, whereby a solution comprising the VP22 polypeptide and oligonucleotide is mixed in solution and is delivered to cells in vitro (See entire document, especially figures 5, 6 and 9; col. 8, line 15 - col. 10, line 38; col. 11, line 62 - col. 12, line 5; col. 12, lines 59-67; claims 1-8).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor

and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 4-14, 17, 19 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of O'Hare et al (USPN 6,184,038), O'Hare et al (WO 97/05265), Hawley-Nelson et al and Schwartz et al, the combination in view of Moyer et al.

The claims are drawn to compositions comprising aggregates of the transport functional domain of VP22 polypeptide (which fragment may comprise amino acid residues 159-301) and an oligonucleotide including an antisense or ribozyme molecule (in a ratio of at least 1:1), which oligonucleotide contains a phosphorothioate internucleoside linkage, which oligonucleotide may alternatively encode a protein or peptide and additionally contain a detectable label, or which polypeptide may be conjugated to a glycoside, or may be a fusion protein, or may be linked by a cleavage susceptible amino acid sequence, and which aggregate may be optionally encapsulated in a liposome, and wherein the aggregate is delivered to target cells. The claims are also drawn to a method of making said aggregated compositions comprising mixing the components, and optionally isolating aggregated particles between 0.1 and 5 microns, and methods of delivering the aggregates to cells in vitro.

O-Hare et al (USPN 6,184,038) teach aggregated compositions and methods of making aggregated compositions comprising a VP22 polypeptide or a fragment thereof having a transport function of VP22 (and which optionally comprise amino acid sequences 159-301 of SEQ ID NO:

12), an oligonucleotide of at least 10 nucleobases, a pharmaceutically acceptable excipient, which aggregated composition has a particle size between 0.1 and 5 microns, whereby a solution comprising the VP22 polypeptide and oligonucleotide is mixed in solution and is delivered to cells in vitro (See entire document, especially figures 5, 6 and 9; col. 8, line 15 - col. 10, line 38; col. 11, line 62 - col. 12, line 5; col. 12, lines 59-67; claims 1-8).

O'Hare et al do not teach an oligonucleotide including an antisense or ribozyme molecule (in a ratio of at least 1:1), which oligonucleotide contains a phosphorothioate internucleoside linkage, which oligonucleotide may alternatively encode a protein or peptide and additionally contain a detectable label, or which polypeptide may be conjugated to a glycoside, or may be a fusion protein, or may be linked by a cleavage susceptible amino acid sequence, and which aggregate may be optionally encapsulated in a liposome, and wherein the aggregate is delivered to target cells, nor optionally isolating aggregated particles between 0.1 and 5 microns, nor the incorporation of a cleavage susceptible amino acid sequence adjacent to the VP22 transport polypeptide within the aggregated compositions.

O'Hare et al (WO 97/05265) teach methods of delivering compositions to target cells in vitro, which compositions comprise at least the functional binding domain of VP22, which may or may not be covalently attached to another peptide or protein, or may optionally be a fusion protein, or may be attached or associated to a polynucleotide, which polynucleotide encodes a protein or peptide. O'Hare et al also teach characterization of the transport domain of VP22

(abstract; page 5, line 18-page 7, line 10; page, line 31-page 16, line 24; page 16, line 26-page 17, line 16; page 25, line 6-page 27, line 34).

Hawley-Nelson et al (USPN 6,376,248) teach methods of forming aggregated compositions and their subsequent delivery to target cells in vitro comprising a VP22 polypeptide with transport function and a nucleic acid of at least 10 nucleobases (in a 1:1 ratio, and having a particle size between .1 to 5 microns), and a pharmaceutically acceptable excipient, and which VP22 polypeptide is optionally part of a fusion protein, and which aggregated compositions are made by mixing the solution comprising a VP22 polypeptide and a polynucleotide, and optionally further comprising mixing and encapsulating the polypeptide and nucleic acid within a liposome (See especially col. 3, line 29-col. 8, line 58; col. 15, line 30-col. 16, line 58; col. 24, line 66-col. 26, line 10).

Schwartz et al (USPN 6,034,135) teach methods of making and using aggregations comprising liposomes, proteins, peptides, glycoproteins and polynucleotides, which polynucleotides include antisense or ribozyme molecules which contain phosphorothioate internucleoside linkages, and which oligonucleotides may be circular, and which oligonucleotides contain a detectable label, and which aggregates are delivered to target cells (column 9, line 57-column 15, line 67; column 19, example B).

Moyer et al (USPN 5,935,777) teach the incorporation of cleavable linkages within various constructs which are destined for target cell, whereby cleavage occurs within the target

cells by the appropriate enzymes, and the joined polypeptides or proteins are released (column 16, lines 40-49).

It would have been obvious to one of ordinary skill in the art to make and use aggregated compositions comprising the binding domain of the VP22 polypeptide and further comprising a polynucleotide, and/or another peptide or protein, because such compositions had been taught previously by O'Hare et al for delivery to target cells. One of ordinary skill in the art would have been motivated to use such compositions for cellular delivery because such transduction domains as the binding domain of VP22 have been used for crossing target cell membranes, as taught previously by O'Hare et al, and therefore the inclusion of VP22 within such compositions was found to enhance the cellular uptake of the compositions, and furthermore also found to enhance localization of the complexes or aggregates within the nuclei of target cells. It would have been obvious to one of ordinary skill in the art to determine a subset of amino acid residues within the VP22 polypeptide, such as the fragment comprising amino acid residues 159-301, which contain transport function because the method and means to determine the amino acid residues required for transport function had been taught previously by O'Hare et al. One of ordinary skill in the art would have expected that incorporation of oligonucleotides and other proteins into such compositions would enhance the cellular uptake of these oligonucleotides and desired effector proteins by the target cells, where the oligonucleotides may then act to inhibit gene expression if they are antisense or ribozymes, or where the oligonucleotides are translated into functional proteins which they encode, which delivered or expressed proteins then exert their effects onto

the target cells upon cellular delivery and uptake. One of ordinary skill in the art would have been motivated to include liposomes within these cell delivery compositions because it was known in the art that liposomes aid in cellular delivery of target oligonucleotides and proteins by fusing with the target cell membranes. Aggregates are an inherent property resulting from the mixing of VP22 polypeptide and oligonucleotides. (Aggregates will also form under CaP transfection conditions.) One of ordinary skill in the art would have expected that aggregates of a particular size are enriched using routine methods of size exclusion known in the art. Furthermore, one of ordinary skill in the art would have expected that aggregates form upon mixing of the amphipathic (cationic) liposomes with the (anionic) polynucleotides and proteins or polypeptides because such aggregation is well known in the art and has been taught previously by Schwartz et al. One of ordinary skill in the art would have been motivated to include a detectable label within the polynucleotide in order to visualize the amount and subcellular localization upon cellular uptake of the composition, since such visualization or detection was a routine matter in the art and had been shown previously by Schwartz et al. It would have been obvious to one of ordinary skill in the art to make and use aggregated compositions comprising liposomes, the transport domain of the VP22 polypeptide and further comprising a polynucleotide and another peptide or protein, because such compositions had been taught previously by O'Hare et al for delivery to target cells. One of ordinary skill in the art would have been motivated to make and use such aggregates further comprising a cleavable linkage between the VP22 polypeptide and another functional component of the aggregated compositions, because such cleavable linkers have been taught

previously by Moyer et al and such cleavable molecules result in dissociation of various components of the aggregates once inside the target cell, whereby the dissociated components are then better able to exert their effect within the cell, unemcumbered by the other components of the aggregates. One of ordinary skill in the art would have expected that such linkages would be cleaved within the target cell by appropriate enzymes, for instance, and the linked protein would then be liberated or released from the aggregate because the tether which held it to the aggregated VP22-polynucleotide-liposome complex has been removed, allowing for the diffusion of the liberated protein or functional component from the aggregated complex, whereby the component then exerts its effect within the cell, free from the complex, as had been taught by Moyer et al.

Therefore, the invention would have prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Allowable Subject Matter

Claim 23 appears free of the prior art searched.

Claim 23 is objected to as being dependent upon a rejected base claim.

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37

C.F.R. § 1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(703) 306-5820.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (703) 308-0447. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (703) 305-3413. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

RAM SHUKLA
PRIMARY EXAMINER

JZ

June 2, 2003